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(54) Title: FLEVOXATE AND DERIVATIVES FOR ERECTILE DYSFUNCTIONS

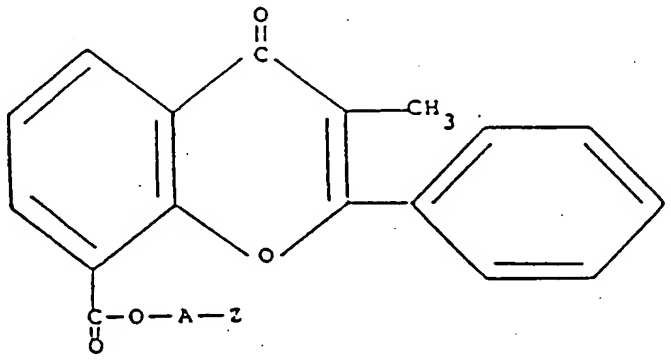
(57) Abstract

Derivatives of 3-methylflavon-8-carboxylic acid are useful for the treatment of penile erectile dysfunctions and for diagnostic methods of erectile impotence.

FLEVOXATE AND DERIVATIVES FOR ERECTILE DYSFUNCTIONS

This invention relates to the use of 3-methyl-flavon-8-carboxylic acid and derivatives thereof for the preparation of a drug for the treatment and for the diagnosis of erectile impotence.

In particular, the invention relates to pharmaceutical compositions for the treatment of erectile impotence containing as the active principle 3-methylflavon-8-carboxylic acid or a derivative thereof of formula I



(I)

wherein:

A is a linear or branched C_1-C_6 alkyl residue and

Z is a dimethylamino, diethylamino, di-n-propylamino, di-isopropylamino, piperidino or morpholino residue,

or pharmaceutically acceptable salts thereof.

Compounds of formula I are known (US Patent No. 2.921.070) and particularly one of them, methylflavone-8-carboxylic acid 2-piperidinoethyl ester (flavoxate) is used in therapy peculiarly for its antispasmodic activity on the smooth muscle of the bladder, ureter and uterus (Ruffmann R., Drug Exp. Clin. Res., 13, 57, (1987)) and it

has also been shown that Flavoxate accumulates preferentially in the genito-urinary tract (Inoue S. et al., Jyakurin Kenkyu, 6, 260, (1975)). Flavoxate is a very well tolerated drug; the large therapeutic index found in preclinical studies (C. Pietra et al., Il Farmaco Ed. Prat., 41, 267, (1986)) and the absence of serious side effects during clinical application, attest its excellent tolerability. Particularly, cardiocirculatory complications have never been reported. 3-methylflavon-8-carboxylic acid(MFCA) is the main metabolite of flavoxate. In terms of pharmacokinetics and - dynamics MFCA is most similar to flavoxate.

Erectile dysfunction is a well known and common disease, of vascular, hormonal, neurogenic or psychogenic origin which causes impaired penile erection.

The insufficient erectile ability of the penis has serious implications for psychological, physical and social well-being of the afflicted individuals. Self confidence in particular, and quality of life in general, are strongly reduced.

Since vascular surgery holds reasonable chances of success only in a limited number of cases, additional attempts to treat this disability have led to various therapeutic approaches. Prosthetic devices that are implanted in the penis to mimic erection or are located outside in the scrotal sac or in an adjacent area to stimulate for instance to trasmitting electrical energy to the nervi erigentes. Pharmacological substances which are also injected directly into the corpora cavernosa, where they increase the inflow of blood and consequently

generate tumescence of the penis, are also used.

However, all these methods have evident disadvantages, causing strong psychological apprehensions and also physical discomfort.

Among the pharmacological substances, 6,7-dimethoxy-1-veratryl isoquinoline (papaverine) and/or alpha blocking agents (as for example phentolamine) are the most frequently used to induce human penile erection and need to be injected direcly into the corpora cavernosa. This procedure has been shown to be most efficient for arteriogenic erectile dysfunctions. Usually the treatment begins with a first injection, performed by a physician as a diagnostic step to differentiate between arteriogenic, psychogenic and the other forms of erectile dysfuntions. In many cases of psychogenic dysfunction this single injection is sufficient to obtain a curative result. If further injections are required, these can be performed either by the physician (office-injection) or by the patient himself (auto-injection).

The major drawback of papaverine and/or alpha blockers in erectile dysfunction is the risk of prolonged and painful erection (priapism) which occurs with a certain frequency.

Further serious complications are of cardiocirculatory nature such as arterial hypotension and hypotensive shock which represent typical toxicity of these agents. In some cases fatalities have been reported. Both, papaverine and alpha blockers have a narrow therapeutic index (ratio between the lethal dose and the effective dose) and absolute or relative overdosing can occur especially

during self injections.

Objects and summary of the invention

The shortcomings of available therapeutic modalities as described above are quite evident.

Useful pharmaceutical agents for the induction and maintainance of penile erection with low toxicity and easy administration, preferably oral, are strongly and essentially needed and hence are the target of intense research.

It has now been found that 3-methylflavon-8-carboxylic acid and compounds of formula I have a relaxing activity on human corpus cavernosum tissue which is comparable to the activity exerted by papaverine during the same experiments. This finding is new and surprising in as much as previously it has been consistently unable to identify any relaxing activity on vascular smooth muscle for flavoxate or MFCA. Any therapeutic activity for erectile dysfunctions has never been reported either.

In fact, numerous investigations in vitro and in vivo, also versus papaverine, had failed to confirm a hypothesized and postulated vasodilating activity of flavoxate. Consequently initial high hopes to develope and market flavoxate as a coronary dilating agent had to be abandoned.

On the other side, the absence of a vasodilating activity, resulted in a complete and most beneficial lack of cardiovascular type side effects.

The results obtained in a pharmacological experimentation using flavoxate and MFCA in comparison with papaverine are hereinbelow reported.

Methods

Human tissue was obtained from patients undergoing penile prothesis implantation.

Biopsies of human corpus cavernosum tissue were obtained in the operating room and immediately placed in chilled (4°C) physiological salt solution of the following millimolar composition: NaCl 118.3; KCl 4.7; $MgSO_4$ 0.6; KH_2PO_4 1.2; CaCl 2.5; $NaHCO_3$ 25.0; Calcium EDTA 0.026 and glucosio 11.1.

The solution is gassed with 95% O_2, 5% CO_2; pH maintained at 7.4 and temperature at 37°C.

Isometric tension measurement

Isometric tension was measured throught the experiment with a tension transducer (Grass FTO3, Quincy, MA). The strips of corpus cavernosum were fixed with silk ties on one end to the electrode support and the other end to a wire connected to the force transducer.

The strips were allowed to equilibrate for a period of approximately three hours. The optimal isometric tension for contraction was determined during this period by stepwise stretching of the tissue followed by contraction with 40 mM KCl or 10^{-6} M phenylephrine. Whenever the potassium or phenylephrine-induced contraction was within 10% of the previous contraction, that tension was considered optimal for isometric contraction. In all tissues, a standardized three hour equilibration period and isometric tension determination study was utilized. In this fashion, the effect of a molecule on a tissue was able to be compared to the effect of the same molecule on different corpus cavernosum

tissues.

To study contraction, the tissue was maintained at the baseline tension. To study relaxion, the tissue was contracted with different agents.

Agents

Drugs were provided in powder form. Stock solutions were made in distilled water. For papaverine and flavoxate the maximal concentration reached 10^{-4} M. At higher concentrations, these molecules would become out of solution. Drugs were introduced to the chamber by cumulative additions in one half log increments.

Calculations

Data is given as means +/- SE. Relaxation are expressed as the percentage relaxation for the maximal relaxation produced by 10^{-3} M sodium nitroprusside.

Results

1) Responses of human corpus cavernosum to papaverine, flavoxate and MFCA at baseline tension.

None of the molecules tested demonstrates any contractile effects of human corpus cavernosum tissue. Two experiments were performed for each molecule.

2a) Responses of human corpus cavernosum (HCC) to papaverine HCl at contracted tension.

Papaverine, at concentration of 10^{-4} M, induced relaxation in HCC contracted with norepinephrine, PG F2 alpha or potassium. Maximal relaxations to the concentration were: 89.9 $\pm$ 3.1%, 90% and 91.6 $\pm$ 1.6% of maximal relaxation, respectively (see figures 1-3). The threshold for the response to this drug was approximately 10^{-5} M.

Tipically the relaxation response to papaverine was slow in onset, requiring more than 10 minutes to reach maximal effect (see figure 1). It was difficult to wash out the effect of papaverine. Repeated washes were required before the tissue recovered the ability to contract normally.

2b) Responses of HCC to flavoxate HCl at contracted tension.

Flavoxate, up to 10^{-4} M, induced relaxation of HCC contracted with norepinephrine, PG F2 alpha or potassium. Maximal relaxations to this concentration were: 73.1 +/- 7.7%, 66 +/- 13.2%, and 55.5 +/- 23% of maximal relaxation, respectively (see figures 1-3). The threshold for the response to flavoxate was approximately 3×10^{-5} M. The relaxation response was slow in onset and several minutes were required before the maximal relaxation response to 10^{-4} M flavoxate was achieved.

2c) Responses of HCC to MFCA Na Salt at contracted tension.

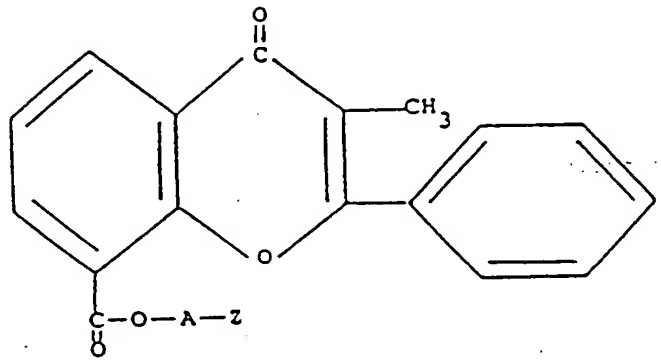
MFCA was easily put into solution and was tested to a concentration of 3×10^{-4} M. It induced relaxation of HCC contracted with norepinephrine, PG F2 alpha or potassium. Maximal relaxations to 3 x 10-4 M was: 54.2 +/- 5.4%, 92.8 +/- 3.5%, and 62% of maximal relaxation, respectively (seee figures 1-3). The threshold of HCC for relaxation by MFCA was 10^{-4} M for norepinephrine and potassium contracted strips and 10^{-5} M for PG F2 alpha contracted tissue.

From what above reported, it is evident how 3-methylflavon-8-carboxylic acid and its basic esters of

formula I, particularly flavoxate, may be conveniently used in human therapy for the treatment of erectile impairments. For this purpose, pharmaceutical compositions suited for the oral, topical or parenteral (intracavernous) administration are provided. The oral administration is particularly convenient for its compliance and it is moreover useful as support therapy in patients who otherwise undergo papaverine or alpha-blockers injection. This regimen allows a reduction of the papaverine and alpha-blocker dosage and improves therefore the safe use of these agents. The doses for an effective treatment of erectile impairments will depend on usual factors such as kind and seriousness of the pathology and patient's weight; nevertheless, a daily oral dose of 1.200 mg proved to be generally effective and well-tolerated. Lower dosage are obviously required in case of intracavernous injection. Transdermal administration forms may also be particularly convenient. The preparation of pharmaceutical forms is within the skill of any expert in the field and it is described for instance in Remington's Pharmaceutical Sciences Handbook, Hack Pub. Co., N.Y. USA.

C L A I M S

1. Use of 3-methylflavon-8-carboxylic acid or a derivative thereof of formula I



(I)

wherein:

A is a linear or branched C_1-C_6 alkyl residue and

Z is a dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, piperidino or morpholino residue,

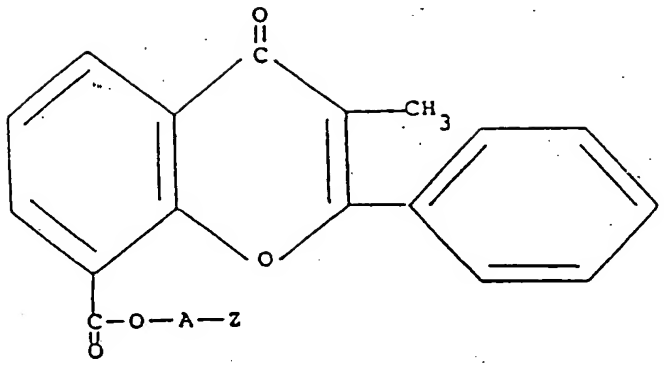
or pharmaceutically acceptable salts thereof,

for the preparation of a medicament for the treatment and diagnosis of erectile dysfunctions.

2. The use of 3-methylflavon-8-carboxylic acid or of a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment and diagnosis of erectile dysfunctions.

3. The use of 2-piperidino-ethyl 3-methylflavon-8-carboxylate or of a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment and diagnosis of erectile dysfunctions.

4. Pharmaceutical compositions for the treatment of erectile dysfunctions comprising an effective amount of 3-methylflavon-8-carboxylic acid or of a salt or derivatives of formula I



(I)

wherein:

A is a linear or branched C_1-C_6 alkyl residue and

Z is a dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, piperidino or morpholino residue,

or pharmaceutically acceptable salts thereof,

in admixture with a suitable carrier.

5. Pharmaceutical compositions according to claim 4, suited for the oral, topical or parenteral administration.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 89/00417

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/35, A 61 K 31/445, A 61 K 31/535

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	Il Farmaco - Ed. Pr., vol. 41, no. 8, 1986, C. Pietra et al.: "Effects of flavoxate on urinary bladder contraction, micturition reflex and urodynamic parameters", pages 267-273, see page 269, lines 32-40; page 272, lines 4-10 --	1-5
Y	J. Urol., vol 136, no. 1, 1986 (Baltimore), K.-P. Juenemann et al.: "Hemodynamics of papaverine- and phentolamine-induced penile erection", pages 158-161, see page 158, left-hand column, lines 5-7; page 160, left-hand column, lines 26-32 --	1-5
Y	Arch. Esp. Urol., vol. 37, suppl. 2, 1984, M. Pavone-Macaluso et al.: "Prostatitis cronicas", pages 689-700, see page 691, right-hand column, line 25 - page 692, left-hand column, line 32; page 697, right-hand column, lines 1-3 --	1-5

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16th June 1989	10 JUIL. 1989

International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	Drugs Exptl. Clin. Res., vol. XIII, no. 1, 1987, Bioscience Ediprint Inc., R. Ruffmann et al.: "Flavoxate, a drug with smooth muscle relaxing activity", pages 57-62, see page 58, right-hand column, lines 6-10; page 59, right-hand column, lines 17-31 --	1-5
Y,P	EP, A, 0266968 (G. COHEN) 11 May 1988, see the whole document --	1-5
A	Medical Aspects of Human Sexuality, vol. 12, no. 11, November 1978 (US), M.G. Fine: "Postcoital dysuria", pages 105-106, see the whole document --	1-5
A	Urol. Int., vol. 35, no. 3, 1980 (CH), A. Zanolla et al.: "Urodynamic response of unstable bladder to flavoxate", pages 176-181, see page 176 ----	1-5

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 8900417
SA 28006

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 05/07/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0266968	11-05-88	AU-A- 8058387	05-05-88
		JP-A- 63132825	04-06-88